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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Carl-Axel Bauer et al.
Serial No. :
Filed : November 13, 2001
Title : NEW USE FOR BUDESONIDE AND FORMOTEROL

Art Unit : 1614
Examiner : R. Cook

Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF JAN TROFAST UNDER 37 CFR §1.132

I, Jan Trofast, declare as follows:

1. I am a co-inventor of the invention claimed in this application.

2. The invention claimed in this application features a method of treating chronic obstructive pulmonary disease (COPD) by administering to a patient, via inhalation, (i) formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and (ii) budesonide, the molar ratio of (i) to (ii) being from 1:2500 to 12:1.

3. I have read the Office Action mailed May 10, 2001 in the parent application (USSN 09/670,457).

4. COPD refers to a group of disorders characterized by a progressive and generally irreversible limitation of airflow. COPD is a common disease in industrialized countries (for example, about 6 % of the men and 4 % of the women over 45 years in the UK are affected) and is responsible for a considerable morbidity and mortality. Most of the patients are smokers. The

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two most important conditions associated with COPD are chronic bronchitis and emphysema. Patients with chronic bronchitis exhibit frequent exacerbations due to recurrent infections.

5. Current treatment of COPD is often unsatisfactory. At present, COPD is often treated only in its more developed stages using a variety of inhaled or orally administered bronchodilators or inhaled anti-cholinergic agents. The problem with these treatments is that none of them has been regarded as effective. Smoking cessation has been shown to decrease the rate of decline in lung function, but the success of smoking-cessation programs is limited.

6. Airway inflammation in COPD differs from such inflammation in asthma. (Jeffery PK, Structural and Inflammatory Changes in COPD: a comparison with asthma. Thorax 1998:53:129-36; attached as Exhibit A). The beneficial influence of oral and inhaled corticosteroids is well established in patients with asthma. However, their usefulness in COPD is much less certain. Around the time of Applicants' invention, researchers were investigating the use of inhaled glucocorticoids such as budesonide in treating COPD. The results, discussed below, generally indicated that inhaled glucocorticoids were much less effective in treating COPD than in treating asthma.

7. One study reported that the overall effect of three years of treatment with budesonide on the forced expiratory volume (FEV) of patients with mild COPD was "quite limited as compared with the beneficial effects of inhaled glucocorticoids in asthma.... The small, overall, one-time beneficial effect on pulmonary function ... must be balanced against the risk of local and systemic side effects." Benefits were found to be only short-term, with no appreciable effect on the long-term progressive decline in lung function. (Pauwels et al., "Long-Term Treatment with Inhaled Budesonide in Persons with Mild Chronic Obstructive Pulmonary Disease Who Continue Smoking," The New England Journal of Medicine, 340:25, pp. 1948-1953, June 24, 1999; attached Exhibit B.)

8. Another study found that the benefits of systemic glucocorticoids in treating acute exacerbations of COPD were much smaller than the benefits of glucocorticoids in the treatment

of severe exacerbations of asthma. (Niewoehner, "Effect of Systemic Glucocorticoids on Exacerbations of Chronic Obstructive Pulmonary Disease," The New England Journal of Medicine, 340:25, pp. 1941-1947, June 24, 1999; attached as Exhibit C.)

9. Several articles at the time mentioned that the current treatments for COPD, including treatment with inhaled steroids, were unsatisfactory, and that new treatments were required. (See, e.g., "Inhaled Steroids in COPD," The Lancet, Vol. 351, pp. 766-767, March 14, 1998, and "COPD: New Developments and Therapeutic Opportunities," Peter Norman, Drug News Perspect 11(7), September 1998; attached as Exhibits D and E, respectively.)

10. In view of this lack of enthusiasm in the field for treatment with budesonide, and also in view of the recognition in the art that asthma and COPD respond differently to treatment with budesonide, it would not have been obvious to the artisan that Carling's composition would be effective in the treatment of COPD. Moreover, in view of the great need for an effective treatment for COPD, if it had been obvious to Carling himself that his composition would have been effective in treating COPD, surely he would have mentioned this in his own disclosure.

11. The Examiner states that, in the absence of unexpected results, it would have been obvious in view of the cited references (U.S. Patent No. 5,795,564 and CA 126:259329) to use budesonide and formoterol together to treat COPD. Applicants respectfully disagree, for the reasons discussed above, and also because Applicants have in fact obtained unexpected results.

12. About 800 patients with moderate to severe COPD were enrolled in a clinical trial. They were divided into four equal groups taking, respectively: budesonide/formoterol (as fumarate dihydrate)(2 x 160/4.5 μg bid, single inhaler), budesonide (2 x 200 μg bid), formoterol (as fumarate dihydrate) (2 x 4.5 μg bid) and a placebo for a period of 12 months. There was a significantly larger number of discontinuations in the placebo group than in the treated groups. The patients were monitored for severe exacerbations, and were tested at each clinical visit (8

times) for Forced Expiratory Volume (FEV_1). These parameters are typically used in evaluating the condition of a patient suffering from COPD.

13. A statistical analysis of the results of this study provided the following data:

Reduction in severe exacerbations (P-value):

Budesonide/formoterol against placebo	0.035
Budesonide/formoterol against formoterol	0.043
Budesonide/formoterol against budesonide	0.385

Improvement in forced expiratory volume (FEV_1) (P-value):

Budesonide/formoterol against placebo	< 0.001
Budesonide/formoterol against budesonide	< 0.001
Budesonide/formoterol against formoterol	0.487

The reduction of severe exacerbations was significantly ($p<5\%$) greater for the patients treated with the budesonide/formoterol combination than for the placebo or the formoterol-treated groups. The study indicates that the number of exacerbations was 24 % lower for the patients treated with the combination than for the patients who received a placebo, and 23 % lower in comparison with formoterol-treated group.

The Forced Expiratory Volume of patients treated with the combination was significantly better ($p<0.1\%$) for the patients treated with the combination than for the placebo or budesonide-treated groups.

14. Together, the results obtained for these parameters indicate a significant improvement in both of the measured parameters for the budesonide/formoterol-treated patients, as compared to the patients treated with either budesonide alone or formoterol alone, over the 12-month period. Thus, the results of this study indicate, unexpectedly, that it is possible to treat even moderate to severe COPD patients with excellent, long-term results using the claimed method.

15. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these

statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Date: 30 Nov. 2001

Jan Trofast